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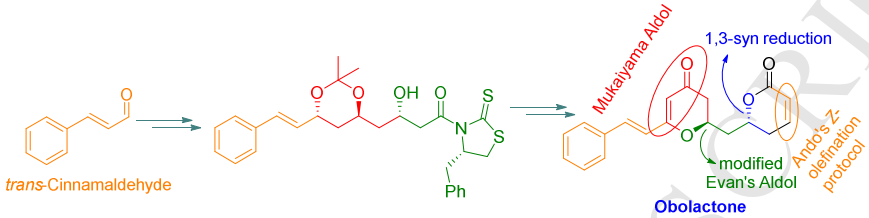

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ABSTRACT

Stereocontrolled total synthesis of obolactone was achieved from *trans*-cinnamaldehyde. The key steps in this synthetic sequence are a asymmetric Mukaiyama Aldol, a Crimmins' modified Evans' Aldol reaction to introduce C2' stereocentre, a nucleophilic addition of potassium salt of mono methyl malonate, a *Z*-olefination using Andos' modified Horner-Wadsworth-Emmons reagent to introduce *Z*-olefin at C3,C4 in the final lactone skeleton, and a tandem deprotection and lactonization.

1. Introduction

6-Substituted-5,6-dihydro-2H-pyran-2-ones are significant structural subunits in many biologically potent natural products.[1] The 5,6-dihydro-α-pyrone units are widely spread in all parts of plants like Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families including leaves, stems, flowers, and fruits.[1] Natural products containing these subunits are recognized for a wide variety of biological activities, such as insect growth inhibition,[2a,b] antimicrobial,[2c] antifungal,[2d] and potent *in vitro* activity against a broad range of cancer cell.[3] The styryl α-pyron skeleton of obolactone **1** is closely related to those of cryptofolione, cryptocaryalactone and fostriecin (**Figure 1**). Most of these styryl α-pyrone containing natural products showed cytotoxicity against human tumour cells.[4]

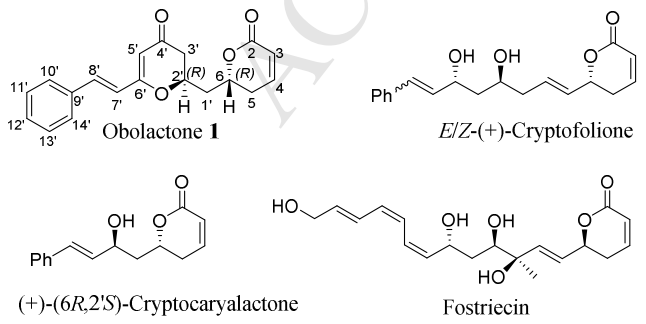

Figure 1: Obolactone **1** and some natural products containing 5,6-dihydro-α-pyrone.

Two dihydro pyrone rings are fused to styryl skeletal, obolactone **1** was isolated from the fruits and the trunk bark of *Cryptocarya obovate* in the Hanoi,Vietnam by Guéritte and co-workers.[5] Obolactone **1** shows a significant activity in vitro cytotoxic assays against the human nasopharyngeal KB cell line with an IC_{50} values of 3 μM.[5] The 2'*R*, 6*R* configuration of obolactone **1** was assigned by X-ray crystallographic analysis and Cotton effect in CD curve.[5] Due to its promising biological activity and skeletal structure, draws the attention of chemists to synthesize. Up until now, there were four syntheses appeared in the literature.[6-9] In continuation of our research for the synthesis of new bioactive molecules,[10] herein we wish to report enantioselective synthesis of obolactone **1**. The Structure-activity relationship of obolactone **1** is under exploration and the results will be reported elsewhere in due course.

In 2006, She and co-workers reported the first asymmetric total synthesis of obolactone **1**, ring-closing metathesis and asymmetric allylation as the key steps of their approach[6]. In Sabitha *et al.*, Prins cyclization and ring-closing metathesis as strategic approach,[7] and the following synthesis from Krishna *et al.* in 2010, Brønsted acid mediated cyclization and Keck allylation as their central approach.[8] Recently, desymmetrization via Wacker oxidation was the significant approach by Bruckner.[9] Here the salient features of our synthetic strategy include: Mukaiyama Aldol using 1,3-bis(trimethylsiloxy)diene **4** (Chan's diene), chiral thiazolidinethione mediated modified Evans' Aldol reaction which is finest technique to introduce stereogenic 1, 3 dihydroxy centers in the chain elongation route, usage of our

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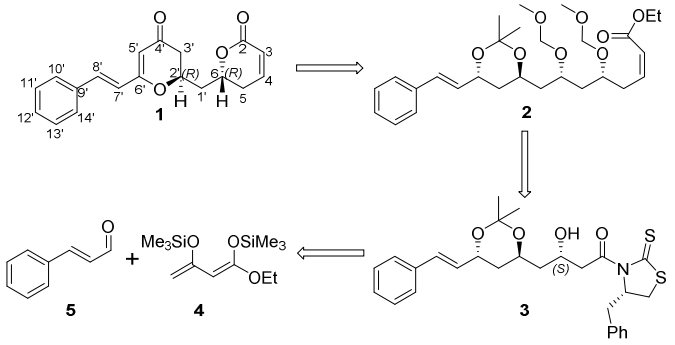
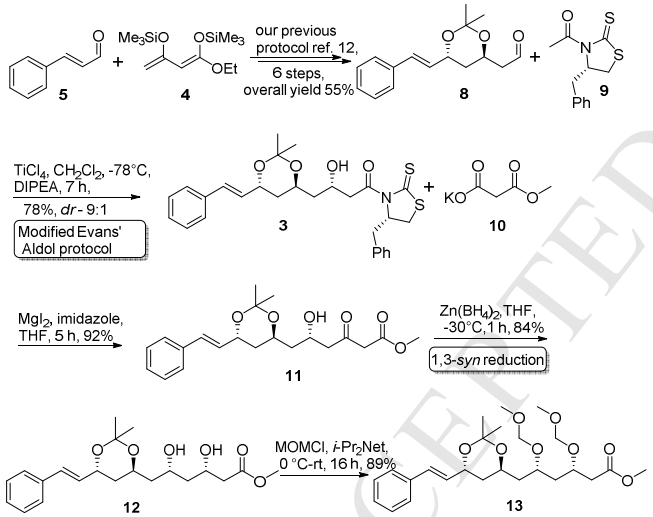
modified chopping method of the chiral auxiliary adduct **3** using magnesium iodide,[11] 1,3-*syn* reduction of *δ*-hydroxy-*β*-keto ester **11** with $Zn(BH_4)_2$ and introducing *Z*-olefin in *α*-pyrone by Andos' diaryl phosphonate. Introduction of double Aldol reaction makes the synthetic strategy highly stereoselective and reduces the number of steps.



Scheme 1. Retrosynthetic strategy of obolactone **1**.

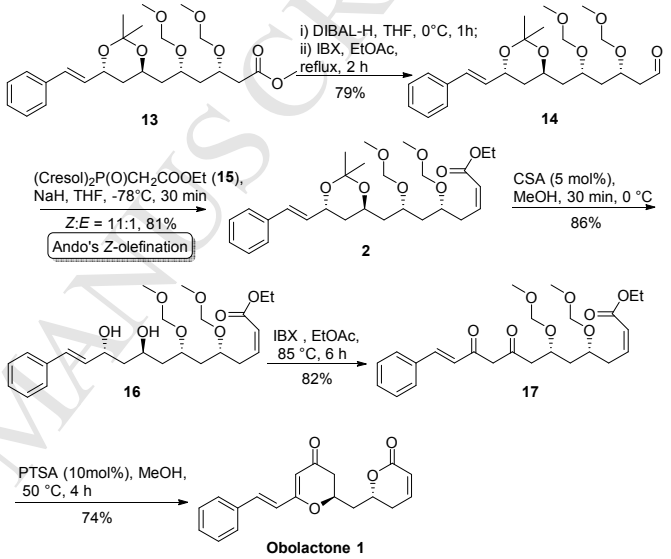
The retrosynthetic pathway of obolactone **1** is depicted in **Scheme 1**, we envisioned that obolactone **1** could be accomplished via sequential operation of selective deprotection of acetonide, oxidation of two 1,3-anti alcohols to 1, 3 diketones and direct lactonization of the *Z*-olefin **2.** *Z*-olefin **2** could be readily obtained from Evans' Aldol adduct **3**. Aldol adduct **3** was envisaged as being accessible from Chan's diene **4** by Mukaiyama asymmetric Aldol onto the commercially available *trans*-cinnamaldehyde **5**.

2. Results and Discussion



Scheme 2. Synthesis of intermediate ester **13**.

Synthesis of obolactone **1** commenced with the transformation of Chan's diene **4** into aldehyde **8** according to our earlier published protocol.[12] To introduce 2'*R*, 6*R* stereocentre in obolactone **1**, herein we executed Crimmins' modified Evans' Aldol reaction with aldehyde **8**. Chiral auxiliaries facilitated asymmetric Aldol reaction is considered to be one of the significant methods for asymmetric C-C bond formation and chain elongation.[13] Most applied type of auxiliaries are the class of chiral oxazolidinones, initially developed in the Evans group,[14] and further modified by other groups.[15] These chiral oxazolidinones has been most effective in the stereoselective construction of numerous chiral building blocks, as well as antibiotics, natural products, and bioactive compounds.[16] Modified Evans' chiral auxiliaries like chiral thiazolidinethiones are become prevalent tools for the modern organic synthesis attributed to their efficient stereoselective transformations.[17] This Crimmins modified imides have been developed to exhibit different complimentary diastereoselectivity compared to the previous ones. Diastereoselective asymmetric acetate Aldol reaction of a chlorotitanium enolate of 4-(*S*)-N-acetyl-4-benzylthiazolidine-2-thione **9**[17c] with aldehyde **8** to introduce the desired stereogenic center at C2', yielding **3** as the major diastereomer (*dr*-9:1) (**Scheme 2**). The subsequent treatment of Aldol adduct **3** with the methyl potassium malonate **10** and MgI_2 in the presence of imidazole resulted in *β*-keto-ester **11**.[11, 17b] Diastereoselective reduction of *δ*-hydroxy-*β*-keto ester **11** with $Zn(BH_4)_2$[18, 12] at -30 °C afforded the desired *syn*-1,3-diol **12** in 84% yield (*syn:anti* 10:1).[19] We be obliged to select the protecting group such a way that it would reduce the number of steps in the synthesis and should be intact during the acetonide deprotection at C6'C4'. Here our choice of protecting group was MOM protection. Thus, the resultant two secondary hydroxyl groups in *syn*-1,3-diol **12** were protected with methoxymethyl chloride (MOMCl) to obtain MOM ether **13** in 89% yield under an extended reaction condition.



Scheme 3. Completion of synthesis of obolactone **1**.

The ester **13** was reduced to alcohol by DIBAL-H in THF at 0 °C, the subsequent oxidation of which using ortho-iodoxybenzoic acid (IBX) in EtOAc reflux provided the corresponding aldehyde **14** in 79% yield. Precursor, $(Cresol)_2P(O)CH_2COOEt$ **15** was obtained through standard method of preparation produced by Ando which allowed access to the (*Z*)-olefins with high stereoselectivity.[20] Andos' modified Horner–Wadsworth–Emmons (HWE) olefination of aldehyde **14** using diaryl phosphonate, $(Cresol)_2P(O)CH_2COOEt$ **15** provided a *α,β*-unsaturated ester **2** favoring the desired *Z*-isomer in 81% yield (*Z*:*E* ratio-11:1) (**Scheme 3**). The *E*:*Z* ratio of the HWE olefination was confirmed based on coupling constant 11.6 Hz and integration values in ^{1}H NMR. Controlled deprotection of acetonide in the *Z*-olefin adduct **2** using camphorsulfonic acid (CSA) in MeOH at 0 °C was proceeded efficiently to afford diol **16** in quantitative yield. Obtained 1,3 diol **16** was oxidised to the corresponding 1, 3 diketone **17** using IBX in EtOAc at 85 °C for 6 h. Finally, the treatment of 1,3 diketone **17** with PTSA in MeOH afforded obolactone **1** in 74% yield.[8] In this asymmetric acetate Aldol synthetic strategy, obolactone **1** was successfully accomplished in 10 steps from aldehyde **8**. ^{1}H and ^{13}C NMR data of obolactone **1** was completely agreed with the literature data.[5, 6]

3. Conclusion

In conclusion, we have completed the stereoselective synthesis of obolactone **1** in a concise approach and the overall yield of this synthetic strategy is about 9.9% from a

commercially available *trans*-cinnamaldehyde **5**. The significance of our synthetic sequence lies in employing a Mukaiyama Aldol addition using Chan's diene, building of the desired stereocentre C2' by a modified form of Evans' thiazolidinethione auxiliary, diastereoselective 1,3-*syn* reduction of *δ*-hydroxy-*β*-keto ester with $Zn(BH_4)_2$, a *Z*-olefination using Andos' modified HWE reagent, and a tandem sequence of MOM deprotection and lactonization. An upgraded method of chopping the Evans' Aldol auxiliary was found to be extremely advantageous, and a selective deprotection of acetonide over MOM with CSA reduced the number of steps in this synthesis.

4. Experimental Section

All reactions were performed under inert atmosphere. All glassware apparatus used for reactions are perfectly oven/flame dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh) unless otherwise mentioned. Analytical thin layer chromatography (TLC) was run on silica gel 60 F254 pre-coated plates (250 μm thickness). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra 75 MHz in $CDCl_3$ solution unless otherwise mentioned, chemical shifts are in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, br = broad.

4.1. 2-((4*R*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)acetaldehyde (8)

To a stirred solution of the ethyl 2-((4*R*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)acetate (2.6 g, 10 mmol) in 40 mL dry THF at 0 °C was slowly added DIBAL-H (25 mL, 25 mmol; 1 M in hexanes) over 20 min. The reaction mixture was stirred at 0 °C for 1 h, then methanol (10 mL) was added dropwise slowly. The resulting solution was poured into aq. potassium sodium tartrate solution (100 mL) and EtOAc (100 mL) and stirred vigorously for l h. The organic layer was separated, and the aqueous layer extracted with further EtOAc (3x100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel gave the corresponding alcohol as a colorless oil.

Add 2-Iodoxybenzoic acid (IBX) (3.78 g, 13.5 mmol) to the stirred solution of above alcohol (2.36 g, 9 mmol) in EtOAc (18 mL) at rt, then heat the reaction mixture to 85 °C, then reflux for 2 h. After completion of reaction, quench with saturated aq. $NaHCO_3$ (50 mL), and the mixture stirred for 20 min at rt. The organic layer was extracted with ethyl acetate (3x100 mL), dried over $MgSO_4$, rotary evaporated, and flash chromatography to give the corresponding aldehyde **8** (1.85 g, 79%) as a colourless oil. R_f = 0.6 (petroleum ether–EtOAc, 3:2). IR (KBr) ν_{max} = 3440, 3026, 2993, 2921, 2854, 2730, 1725, 1654, 1495, 1381, 1262, 1200, 1165, 1137, 1097, 968, 874, 750, 695, 523 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.9 Hz, 1H), 7.40-7.19 (m, 5H), 6.56 (dd, *J* = 16.0, 1.3 Hz, 1H), 6.21 (dd, *J* = 16.0, 6.1 Hz, 1H), 4.54 (dtd, *J* = 9.4, 6.3, 1.5 Hz, 1H), 4.44 (dtd, *J* = 10.7, 5.9, 5.2, 3.0 Hz, 1H), 2.67 (ddd, *J* = 16.7, 8.1, 2.3 Hz, 1H), 2.52 (ddd, *J* = 16.6, 4.8, 1.6 Hz, 1H), 1.98 (ddd, *J* = 12.9, 9.0, 5.9 Hz, 1H), 1.81 (ddd, *J* = 12.9, 9.4, 6.2 Hz, 1H), 1.45 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.79, 136.54, 130.48, 129.35, 128.48, 127.66, 126.43, 100.69, 67.45, 61.98, 49.14, 37.59, 25.29, 24.74. EI-MS: *m/z* 261[M$^+$+H].

4.2. (*S*)-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-4-((4*S*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)-3-hydroxybutan-1-one (3)

In a dry round bottom flask under argon atmosphere, (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone **9** (1.26 g, 5 mmol) was dissolved in CH_2Cl_2 (10 mL), then cooled to 0 °C. A solution of $TiCl_4$ (0.66 mL, 6 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture, and the thick suspension was stirred for 20 minutes, upon which diisopropylethylamine (1.07 mL, 6 mmol) was added dropwise at 0 °C. The solution after stir for 20 min at same temperature, then cooled to -78 °C and to the reaction mixture was added freshly prepared aldehyde **8** (1.3 g, 5 mmol) in CH_2Cl_2 (10 mL). The reaction was further stirred for 1 h, then quenched with saturated NH_4Cl, and warmed to rt. The layers were separated and the aqueous layer was extracted CH_2Cl_2 (3x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 7:3) to provide the product **3** (1.98 g, 78%) as a yellow liquid. R_f = 0.4 (petroleum ether–EtOAc, 7:3). IR (KBr) ν_{max} = 3424, 3027, 2992, 2940, 1754, 1650, 1492, 1448, 1381, 1260, 1199, 1164, 1136, 1078, 966, 876, 748, 694, 523 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.16 (m, 10H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.19 (ddd, *J* = 16.0, 6.2, 1.0 Hz, 1H), 5.29-5.21 (m, 1H), 4.62-4.51 (m, 1H), 4.35-4.16 (m, 1H), 3.94-3.88 (m, 1H), 3.68 (d, *J* = 11.1, 2.8 Hz, 1H), 3.43-3.32 (m, 2H), 3.23 (dd, *J* = 12.3, 4.1 Hz, 1H), 3.03 (dt, *J* = 10.4, 2.0 Hz, 1H), 2.84 (d, *J* = 11.4 Hz, 1H), 2.67-2.49 (br, 1H), 1.89-1.61 (m, 4H), 1.55 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.75, 172.18, 136.45, 136.37. 130.70, 130.58, 129.50, 129.25, 128.35, 127.59, 126.35, 100.79, 69.76, 68.78, 64.15, 63.40, 46.38, 43.31, 37.72, 36.55, 32.14, 25.52, 24.21. MS (ESI): *m/z* = 534 [M + Na]$^+$. HRMS: calcd. for $C_{28}H_{33}NO_4S_2Na$ [M + Na]$^+$: 534.17487: found: 534.17478.

4.3. Methyl (*S*)-6-((4*S*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)-5-hydroxy-3-oxohexanoate (11)

To a solution of thiazolidinethione Aldol adduct **3** (5 mmol, 1.0 equiv) in THF (20 mL) was added methyl potassium malonate **10** (10 mmol, 2.0 equiv) followed by MgI_2 (5 mmol, 1.0 equiv) under Argon. The suspension was stirred at rt for 30 min, then imidazole (5 mmol, 1.0 equiv) was added in one portion, and the reaction mixture was stirred at rt for 5 h. After completion, the reaction was diluted with EtOAc (100 mL), washed with 0.5 M HCl (50 mL), and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were then washed with 0.5 M $NaHCO_3$ (50 mL). Finally, the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a light yellow oily liquid. The resulting crude mixture was purification by flash chromatography (petroleum ether–EtOAc, 3:2) to afford the pure *δ*-hydroxy-*β*-ketoester **11** (1.73 g, 92%). R_f = 0.3 (petroleum ether–EtOAc, 7:3). IR (KBr) ν_{max} = 3478, 2992, 2923, 2854, 1745, 1715, 1652, 1438, 1381, 1324, 1262, 1200, 1163, 1093, 968, 937, 748, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.12 (m, 5H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.15 (ddd, *J* = 16.0, 6.2, 4.7 Hz, 1H), 4.55 (ddd, *J* = 9.8, 6.6, 2.7 Hz, 1H), 4.42-4.15 (m, 2H), 3.73 (s, 3H), 3.51 (d, *J* = 7.0 Hz, 2H), 3.08 (br, 1H), 2.83-2.58 (m, 2H), 1.77-155 (m, 4H), 1.54 (d, *J* = 5.3 Hz, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.23, 167.35, 136.45, 130.70, 129.50, 128.35, 127.59, 126.35, 100.29, 69.91, 65.89, 64.15, 52.25, 49.80, 49.49, 42.15, 36.88, 25.22, 24.63. MS (ESI): *m/z* = 399 [M + Na]$^+$.

HRMS: calcd. for $C_{21}H_{28}O_6Na$ [M + Na]$^+$: 399.17781: found: 399.17671.

4.4. Methyl (3*S*,5*R*)-6-((4*S*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)-3,5-dihydroxyhexanoate (12)

A freshly prepared solution of $Zn(BH_4)_2$ in ether (~1M, 5 mL) was added to a solution of *δ*-hydroxy-*β*-ketoester **11** (1.5 g, 4 mmol) in ether (20 mL) at -30 °C and the reaction mixture was stirred for 1 h at this temperature. The reduction was almost completed within 10 min. The reaction was quenched by the successive addition of water (10 mL) and aqueous 0.1N HCl (20 mL), and the mixture was extracted with ether (3x100 mL). The combined ether layers was washed with saturated aqueous $NaHCO_3$ (50 mL) solution and brine, then dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica gel (petroleum ether–EtOAc, 1:1) to obtain *syn*-1,3-diol **12** (1.27 g, 84%) with *dr*-10:1. R_f = 0.3 (petroleum ether–EtOAc, 3:2). IR (KBr) ν_{max} = 3449, 2925, 2859, 1732, 1641, 1436, 1381, 1263, 1201, 1164, 1090, 927, 935, 877, 750, 694, 522 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.17 (m, 5H), 6.57 (d, *J* = 16.0 Hz, 1H), 6.23 (dt, *J* = 16.0, 5.7 Hz, 1H), 4.63-4.46 (m, 1H), 4.42-4.16 (m, 2H), 3.88-4.04 (m, 1H), 3.71 (s, 3H), 3.35-3.14 (br, 1H), 2.74-2.47 (m, 2H), 1.73-1.50 (m, 7H), 1.50-1.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.61, 136.47, 130.89, 129.32, 128.46, 127.70, 126.47, 100.74, 71.40, 69.94, 68.73, 66.44, 51.68, 43.13, 42.75, 41.59, 37.12, 25.49, 24.83. MS (ESI): *m/z* = 401 [M + Na]$^+$. HRMS: calcd. for $C_{21}H_{30}O_6Na$ [M + Na]$^+$: 401.1935: found: 401.1925.

4.5. Methyl (3*S*,5*R*)-6-((4*S*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)-3,5-bis(methoxymethoxy)hexanoate (13)

To a solution of **12** (1.13 g, 3 mmol) in dry CH_2Cl_2 (6 mL) were added *i*-Pr_2NEt (3.16 mL, 18 mmol) and methoxymethyl chloride (MOMCl, 0.905 mL, 12 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. Then the reaction was quenched with sat. aqueous NH_4Cl and the whole was extracted with EtOAc (3x75 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether–EtOAc, 7:3) to give **13** (1.25 g, 89%) as a thick liquid. R_f = 0.3 (petroleum ether–EtOAc, 7:3). IR (KBr) ν_{max} = 2991, 2946, 2853, 1739, 1600, 1440, 1379, 1200, 1151, 1100, 1035, 969, 918, 748, 695, 522 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.16 (m, 5H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.16 (dd, *J* = 16.0, 6.1 Hz, 1H), 4.72-4.60 (m, 4H), 4.59-4.46 (m, 1H), 4.23-4.04 (m, 2H), 3.95-3.81 (m, 1H), 3.69 (d, *J* = 1.2 Hz, 3H), 3.41 (s, 3H), 3.36 (s, 3H), 2.72-2.45 (m, 2H), 2.03-1.82 (m, 2H), 1.79-1.56 (m, 4H), 1.51 (d, *J* = 3.4 Hz, 3H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.69, 136.58, 130.64, 129.76, 128.41, 127.58, 126.44, 100.36, 96.35, 95.87, 72.27, 71.70, 70.10, 67.67, 55.77, 55.61, 51.52, 40.85, 40.11, 39.46, 38.22, 25.86, 24.94. MS (ESI): *m/z* = 489 [M + Na]$^+$. HRMS: calcd. for $C_{25}H_{38}O_8Na$ [M + Na]$^+$: 489.2458: found: 489.2444.

4.6. Ethyl (5*R*,7*R*,*Z*)-8-((4*S*,6*R*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)-5,7-bis(methoxymethoxy)oct-2-enoate (2)

To a stirred solution of the ester **13** (932 mg, 2 mmol) in dry THF (10 mL) at 0 °C was slowly added DIBAL-H (5 mL, 5 mmol; 1 M in hexanes) over 20 min. The reaction mixture was stirred at 0 °C for 1 h, then MeOH (10 mL) was added dropwise slowly. The resulting solution was poured into aqueous sodium potassium tartrate solution (15 mL) and EtOAc (50 mL) and stirred vigorously for l h. The organic layer was separated and the aqueous layer extracted with further EtOAc (3x75 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude extract was purified by flash column chromatography (petroleum ether–EtOAc, 1:1) to give corresponding alcohol as a thick liquid. R_f = 0.3 (petroleum ether–EtOAc, 1:1). Add IBX (767 mg, 1.74 mmol) to the stirred solution of above alcohol (180 mg, 0.40 mmol) in EtOAc (10 mL) at rt, then heat the reaction mixture at 85 °C reflux for 2 h and check TLC for the completion of reaction. After completion of reaction, quench with saturated aqueous $NaHCO_3$ (20 mL) and the mixture stirred for another 30 min. The organic layer was extracted with ethyl acetate (3x75 mL), dried over $MgSO_4$ and rotary evaporated to give aldehyde **14** (689 mg, 79%) as a colourless oil. R_f= 0.5 (petroleum ether–EtOAc, 3:2). This aldehyde used for further reaction without purification.

To a stirred suspension of NaH (60% dispersion in oil) (48 mg, 1.2 mmol) in dry THF (5 mL) was added a solution of $(Cresol)_2P(O)CH_2COOEt$ phosphonate **15** (417 mg, 1.2 mmol) in dry THF (2.5 mL) at -78 °C under argon, and the reaction mixture was stirred for 30 min at the same temperature. Then a solution of the aldehyde **14** (436 mg, 1.0 mmol) in THF (2.5 mL) was added dropwise, and the reaction mixture was stirred at −78 °C for about 30 min. After completion of reaction, brought the reaction mixture to −35 °C and quenched with aq. ammonium chloride. The reaction mixture was extracted with CH_2Cl_2 (3x50 mL), and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by column chromatography (petroleum ether–EtOAc, 7:3) to give (*Z*)-*α*,*β*-unsaturated ester **2** (409 g, 81%) as a thick liquid. R_f = 0.3 (petroleum ether–EtOAc, 4:1). IR (KBr) ν_{max} = 2926, 2856, 1727, 1647, 1456, 1377, 1278, 1170, 1106, 1036, 953, 758, 700, 514 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.21 (m, 5H), 6.59 (dt, *J* = 16.6, 1.3 Hz, 1H), 6.34 (dtt, *J* = 10.3, 6.8, 3.3 Hz, 1H), 6.17 (ddd, *J* = 16.0, 6.3, 1.6 Hz, 1H), 5.88 (dt, *J* = 10.3, 1.8 Hz, 1H), 4.73-4.63 (m, 4H), 4.57-4.50 (m, 1H), 4.32-4.06 (m, 4H), 3.94-3.79 (m, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 3.07-2.83 (m, 2H), 1.96-1.84 (m, 2H), 1.73-1.55 (m, 4H), 1.51 (d, *J* = 3.5 Hz, 3H), 1.46-1.42 (m, 3H), 1.30-1.22 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.12, 145.47, 136.56, 131.38, 129.76, 128.37, 126.39, 125.26, 121.41, 100.33, 95.85, 95.34, 73.84, 71.91, 70.08, 65.44, 61.88, 55.62, 55.58, 42.19, 39.31, 37.20, 33.66, 25.38, 24.77, 14.17. MS (ESI): *m/z* = 529 [M + Na]$^+$. HRMS: calcd. for $C_{28}H_{42}O_8Na$ [M + Na]$^+$: 529.27719: found: 529.27542.

4.7. Ethyl (2*Z*,5*R*,7*S*,9*R*,11*R*,12*E*)-9,11-dihydroxy-5,7-bis(methoxymethoxy)-13-phenyltrideca-2,12-dienoate (16)

CSA (4 mg, 5 mol%) was added to a solution of (*Z*)-*α*,*β*-unsaturated ester **2** (151 mg, 0.30 mmol) in MeOH (3 mL) and the mixture was stirred at 0 °C for 30 min. After completion of reaction, extracted with ether (2x50 mL). The ether extract was washed with saturated aq. $NaHCO_3$ solution, and NaCl solution, then dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 1:1) to afford diol **16** (120 mg, 86%) as a thick liquid. R_f = 0.3 (petroleum ether–EtOAc, 1:1). IR (KBr) ν_{max} = 3446, 2925, 2856, 1723, 1634, 1454, 1278, 1035, 762, 502 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.18 (m, 5H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.31 (dtd, *J* = 11.5, 7.3, 2.0 Hz, 1H), 6.21 (dd, *J* = 15.9, 6.3 Hz, 1H), 5.88 (dq, *J* = 11.5, 1.9 Hz, 1H), 4.67 (ddt, *J* = 13.8, 12.4, 5.6 Hz, 4H), 4.56 (q, *J* = 4.6, 3.9 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.10-3.88 (m, 2H), 3.86-3.73 (m, 1H), 3.38 (d, *J* = 1.1 Hz, 3H), 3.36 (s, 3H), 3.03-2.81 (m, 2H), 1.97-1.84 (m, 1H), 1.82-1.54 (m, 4H), 1.32-1.23 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.28, 145.20, 136.75, 131.93, 129.49, 128.41, 127.40, 126.34, 121.66, 95.30, 95.15, 73.66, 72.71, 70.89, 68.47, 59.95, 55.79, 55.68, 43.70, 42.34, 39.54, 33.52, 14.14. MS (ESI):

m/z = 489 [M + Na]$^+$. HRMS: calcd. for $C_{25}H_{38}O_8Na$ [M + Na]$^+$: 489.2458 : found: 489.2445.

4.8. Ethyl (2*Z*,5*R*,7*R*,12*E*)-5,7-bis(methoxymethoxy)-9,11-dioxo-13-phenyltrideca-2,12-dienoate (17)

Add IBX (560 mg, 2 mmol, 5 equiv.) to the stirred solution of diol **16** (187 mg, 0.40 mmol, 1 equiv.) in ethyl acetate (5 mL) at rt, then heat the reaction mixture at 85 °C reflux for 6 h and check TLC for the completion of reaction. After completion of reaction, quench with saturated aqueous $NaHCO_3$ (20 mL), and the mixture stirred for 20 min. The organic layer was extracted with EtOAc (3x75 mL), dried over $MgSO_4$ and rotary evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 3:2) to give the corresponding diketone **17** (152 mg, 82%) as a colourless thick liquid. R_f =0.3 (petroleum ether–EtOAc, 7:3). $[\alpha]_D^{20}$ = -42 (*c* = 0.5, $CHCl_3$). IR (KBr) ν_{max} = 2923, 2852, 1716, 1638, 1586, 1445, 1379, 1217, 1149, 1098, 1031, 917, 771, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.47 (m, 3H), 7.45-7.31 (m, 3H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.33 (dt, *J* = 11.5, 7.3 Hz, 1H), 5.89 (dt, *J* = 11.5, 1.9 Hz, 1H), 5.70 (d, *J* = 3.5 Hz, 1H), 4.68 (d, *J* = 9.4 Hz, 4H), 4.19 (p, *J* = 7.0 Hz, 2H), 3.88 (dt, *J* = 12.2, 6.0 Hz, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 3.09-2.85 (m, 2H), 2.66 (dd, *J* = 6.3, 1.8 Hz, 2H), 1.95 (dt, *J* = 13.8, 6.7 Hz, 1H), 1.71 (dt, *J* = 14.4, 6.1 Hz, 2H), 1.32-1.24 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.81, 177.22, 166.21, 145.26, 139.94, 135.02, 129.91, 128.88, 127.91, 122.75, 121.71, 101.75, 95.87, 95.36, 73.62, 72.19, 59.92, 55.81, 55.68, 45.76, 39.76, 33.52, 29.69, 14.25. MS (ESI): *m/z* = 485 [M + Na]$^+$. HRMS: calcd. for $C_{25}H_{34}O_8Na$ [M + Na]$^+$: 485.2146: found: 485.2148.

4.9. Obolactone (1)

To a stirred solution of diketone **17** (46 mg, 0.1 mmol) in MeOH was added PTSA (2 mg, 0.01 mmol) under an N_2 atmosphere. Heat the reaction mixture to 50 ^{o}C and stir at this temperature for 4 h. After completion of the reaction, quenched with solid $NaHCO_3$ and filtered off, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to afford obolactone **1** as a yellow solid (22 mg, 74%). $[\alpha]_D^{20}$ = +247 (*c* = 0.1, $CHCl_3$). IR (KBr) ν_{max} = 2927, 2853, 1726, 1650, 1447, 1377, 1279, 1211, 1149, 1098, 1035, 974, 917, 750, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.49 (m, 2 H), 7.45–7.26 (m, 4 H), 6.95–6.82 (m, 1 H), 6.53 (d, *J* = 16.0 Hz, 1 H), 6.09 (dt, *J* = 9.7, 1.6 Hz, 1 H), 5.62 (s, 1 H), 4.85–4.64 (m, 2 H) 2.63–2.45 (m, 5 H), 2.21–1.98 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.02, 167.97, 163.66, 144.64, 137.40, 134.75, 129.66, 128.64, 127.43, 121.54, 121.02, 106.27, 75.67, 74.49, 41.32, 39.18, 29.27. MS (ESI): *m/z* = 311 [M + H]$^+$. HRMS: calcd. for $C_{19}H_{19}O_4$ [M + H]$^+$: 311.1278: found: 311.1275.

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Supplementary data

^{1}H and ^{13}C NMR spectra of compounds are available.

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